

# Epidemiologic, Clinical, and Laboratory Features of Coxsackie B1-B5 Infections in the United States, 1970-79

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The late Dr. Klein was Director, Service of Virology, Nassau County Medical Center, East Meadow, N.Y., 1970-79. His contributions were a key element of this work.

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## Synopsis .....

In the period 1970 through 1979, the Coxsackie B1, B2, B3, B4, and B5 viruses constituted 24 percent of more than 18,000 enteroviruses isolated and reported through national surveillance. Young children, especially males, were most frequently affected: 48 percent of the national surveillance population were less than 5 years of age, including 30 percent who were less than 1 year old. Among the most frequently reported clinical syndromes associated with B infection were meningitis (in 56 percent of patients with B1-B5 infections), encephalitis (in 15 percent), and respiratory tract disease (in 14 percent). Carditis, a well-known B syndrome, was reported with only 2 percent of B1-B5 infections. Like most

enteroviral agents, Group B viruses were isolated primarily during the summer: 87 percent of all these isolations were made during the 5 months from June through October. Although B2, B3, and B4 viruses were isolated at relatively uniform levels each year, B1 and B5 viral illnesses occurred nationwide as explosive epidemics only in certain years.

A separate population of B-infected patients, identified by the Nassau County Medical Center (NCMC) Virus Laboratory, East Meadow, N.Y., during the same 10-year period, was studied to compare epidemiologic characteristics and to evaluate in greater detail clinical and laboratory features of B infections. Because of more active solicitation of specimens for testing, ascertainment in the NCMC system was more complete. The most frequently reported clinical findings at NCMC included fever (97 percent of cases), which was biphasic in 27 percent; pharyngitis (85 percent); vomiting (56 percent); headache (49 percent); other respiratory signs and symptoms (44 percent); diarrhea (40 percent); abdominal pain (33 percent); rash (31 percent); and otitis (28 percent). Rash was more frequently associated with younger than with older age groups ( $P < .01$ ) for all B agents. Overall, throat (T) and rectal (R) swabs had the highest B-positivity rates among known infected patients (83 percent for T and 78 percent for R). Only for T was the positivity rate correlated with the interval between onset of illness and obtaining the specimen ( $P < .05$ ). B agents grew most quickly from T specimens, but most reliably from R specimens. On the basis of these data, the authors recommend that both T and R specimens be obtained from every patient for whom prompt and reliable laboratory diagnosis of B infection is sought.

To the authors' knowledge, these results from 10 years of national surveillance represent the largest surveillance summary of Coxsackie B viruses to date in the literature. Comparison of these results with those reported over the same 10 years by NCMC reflects differences that arise mostly because of differences in ascertainment systems.

THE COXSACKIE B VIRUS GROUP constitutes 6 of the 68 known enteroviral agents. The spectrum of disease associated with B infections ranges from asymptomatic or minor febrile illness and gastroenteritis to more severe syndromes including aseptic meningitis, carditis, and often fatal encephalomyocarditis of the newborn (1-34). The distribution of clinical syndromes detected depends in large part on the population of patients selected for

study. Because virologic studies may often be regarded as not cost-beneficial, clinicians may submit specimens only from the most ill patients, thus distorting the epidemiology and true distribution of clinical features of these agents.

This paper reports data on the Group B viruses from two different patient populations, comparing clinical, epidemiologic, and laboratory features of B1, B2, B3,

B4, and B5 infection. One patient population consisted of 4,219 cases (4,391 isolates) of B1-B5 infection reported to the Centers for Disease Control (CDC), from 1970 through 1979, through the national Enterovirus Surveillance Program (ESP). (Six Coxsackie B6 isolates were also reported, but because of the small number and the impracticality of epidemiologic interpretation, these reports have been excluded from this analysis.) The second patient population consisted of 602 cases of B1-B5 infection (624 isolates) detected at a single regional hospital-based laboratory, the Nassau County Medical Center (NCMC) Virus Laboratory, East Meadow, N.Y., during the same period. In both study populations, only cases confirmed by virus isolation are included in this report.

## Methods

**ESP and NCMC reporting.** Details of ESP reporting have been described previously (13). Participating State health department laboratories and other laboratories voluntarily submit monthly reports of their enteroviral isolates to CDC, along with available demographic and clinical information. Patient selection and laboratory isolation procedures undoubtedly vary from State to State. Data from this nonuniform population must therefore be interpreted with great care.

The NCMC Virus Laboratory serves its own 600-bed county medical center, 14 nearby hospitals, and some private clinicians. Overall, approximately 78 percent of the specimens received by this laboratory were received from patients seen at NCMC. Of these specimens, 34 percent were from inpatients and 66 percent from outpatients.

The patient population in the NCMC study group represents a much more uniformly selected group than that reported through the ESP. The Virus Laboratory actively seeks throat swabs from all febrile pediatric outpatients seen at NCMC, as well as throat and rectal swabs from all adult inpatients and outpatients suspected of having a viral illness and from all hospitalized pediatric patients, including newborns, regardless of the reason for admission. Whereas pediatric specimens are consistently submitted, very few specimens are received from adult patients seen at NCMC. The most frequently submitted specimens from any patient are throat and rectal swabs. (Other types of specimen are nasopharyngeal swabs and cerebrospinal fluid.) The laboratory records the available demographic and clinical information on all patients for whom specimens are submitted. In addition, for this report, records of all patients with B isolates were examined individually to extract a more complete history of clinical and laboratory findings.

Since 1970, the NCMC Virus Laboratory has routinely inoculated material from specimens into rhesus monkey kidney and human embryonic kidney tissue culture cells. African green monkey kidney and cynomolgus monkey kidney cells have occasionally been used. Laboratory results are available for all patients for whom specimens are submitted, including those from whom no virus was isolated.

This report includes all results for patients with B1-B5 virus isolated from at least one anatomic source.

## Epidemiologic Results

**Agents isolated.** From 1970 through 1979, CDC received reports from ESP of 4,391 isolates of B1-B5 from 4,219 patients (table 1). The most frequently isolated agent was B5 (43 percent of isolates), followed by B2 (20 percent), B4 (18 percent), B3 (13 percent), and B1 (6 percent). B5 was the second most frequently isolated agent in overall ESP reporting from 1970 through 1979, following echovirus 9 with 2,238 isolates (13).

In contrast to the ESP reports, the most frequently isolated agents at NCMC were B4 (27 percent of isolates), B2 (24 percent), B3 (23 percent), B5 (20 percent), and B1 (6 percent).

In the NCMC population, B5 produced an extensive outbreak of the disease: 107 (84 percent) of the total number of B5 cases in the 10-year study period occurred in 1972. The epidemiologic curve for the NCMC population was virtually identical to that for the ESP population and reflected the nationwide epidemic that occurred in 1972. B3 produced two significant epidemics on Long Island in 1973 and 1976; 91 (64 percent) of all B3 cases identified in the 10-year period occurred during these 2 years. These local epidemics did not correspond exactly to the overall national pattern; however, the pattern reflects the sum of several local outbreaks and is not necessarily a true nationwide pattern.

**Seasonal distribution.** In the ESP system, the majority of B isolations were reported during the summer and early autumn. From June through October, the average monthly number of isolations was 9.6 times higher than that during the remaining 7 months. Of those isolations for which the month was known, 3,120 (87 percent) were reported during the peak 5 months and 455 (13 percent) during the less active period. This seasonal distribution was similar for all B agents except B3, which was isolated significantly more frequently during the cooler months (from January through April, 12 percent of isolations reported were B3 versus 4 percent overall,  $\chi^2 = 12.5$ ,  $P < .001$ ).

The NCMC system recorded a similar seasonal distribution of B isolations, with most outbreaks occurring from June to September.

Table 1. Number of Coxsackie B1–B5 isolates reported through national surveillance and by the Nassau County Medical Center, by agent and year, 1970–79

Year	Isolates reported through national surveillance						Isolates reported by Nassau County Medical Center					
	B1	B2	B3	B4	B5	Total	B1	B2	B3	B4	B5	Total
1970.....	10	30	18	36	4	98	...	3	...	...	...	3
1971.....	22	89	30	53	6	200	2	10	13	5	...	30
1972.....	66	150	91	107	1,367	1,781	2	3	4	12	107	128
1973.....	9	73	75	96	295	548	...	37	34	22	2	95
1974.....	4	87	54	34	2	181	...	15	3	3	1	22
1975.....	2	54	30	76	2	164	...	12	8	11	...	31
1976.....	18	137	99	120	5	379	2	7	57	51	1	118
1977.....	103	35	90	21	70	319	17	6	11	1	3	38
1978.....	7	36	38	92	87	260	1	4	10	4	7	26
1979.....	22	206	31	152	50	461	15	50	3	59	6	133
Total.....	263	897	556	787	1,888	4,391	39	147	143	168	127	624

Table 2. Age and sex distribution of patients with Coxsackie B1–B5 infections reported through national surveillance and by the Nassau County Medical Center, 1970–79<sup>1</sup>

Age (years)	National surveillance				Nassau County Medical Center			
	Male	Female	Total		Male	Female	Total	
			Number	Percent			Number	Percent
0–4.....	1,083	754	1,837	48	230	139	369	61
5–9.....	403	205	608	16	70	50	120	20
10–14.....	226	161	387	10	41	27	68	11
15–19.....	141	83	224	6	13	6	19	3
20–24.....	96	109	205	5	4	5	9	1
25–29.....	107	108	215	6	7	2	9	1
30–34.....	82	33	115	3	4	7	11	2
35–39.....	49	27	76	2				
40–49.....	48	31	79	2				
50 or more.....	43	63	106	3				
Total.....	2,278	1,574	3,852	<sup>2</sup> 101	369	236	605	<sup>2</sup> 99
Percent.....	59	41		100	61	39		100

<sup>1</sup> Includes only cases for which both age and sex were reported.

<sup>2</sup> Does not add to 100 because of rounding.

**Age distribution.** B agents were isolated most frequently from young pediatric patients (table 2). In the ESP population, of those isolations for which the patient's age and sex were known, 1,837 (48 percent) were from children 0–4 years of age, including approximately 30 percent from infants less than 1 year old. This trend held for all 5 B agents reported on here and ranged, in the < 1-year age group, from 28 percent (B5) to 37 percent (B1). Isolates from adults  $\geq$  30 years old uniformly constituted 7–11 percent of each group.

Among the ESP cases, the age distribution for each of the reported syndromes differed from the overall age distribution of B-infected patients. The 0–4 year age group constituted 48 percent of the overall population, but 73 percent of all paralytic cases ( $P < .05$ ); 69 percent

of rash-illness cases ( $P < .05$ ); 62 percent of cases of undifferentiated fever ( $P < .05$ ); 61 percent of patients with miscellaneous known syndromes ( $P < .001$ ); and 51 percent of meningitis cases ( $P < .05$ ). On the other hand, older patients tended to predominate in the remaining syndromes. Those 5–14 years old constituted 25 percent of the overall population and 39 percent of patients with respiratory disease ( $P < .001$ ). Patients 10–24 years old were 20 percent of the overall population and 29 percent of encephalitis cases ( $P < .001$ ). Those 15–39 years old constituted 22 percent of the overall population and 34 percent of carditis cases ( $P < .01$ ).

As in the ESP population, the age distribution among NCMC patients was skewed toward the younger ages: 61

Table 3. Distribution of clinical syndromes associated with Coxsackie B1–B5 infections reported through national surveillance and by the Nassau County Medical Center (NCMC), 1970–79

Syndrome	B1		B2		B3		B4		B5		Total	
	No.	Percent <sup>2</sup>	No.	Percent <sup>2</sup>	No.	Percent <sup>2</sup>	No.	Percent <sup>2</sup>	No.	Percent <sup>2</sup>	No.	Percent <sup>2</sup>
<i>National surveillance</i>												
Paralysis .....	1	1	4	1	2	1	1	1	8	1	16	1
Encephalitis .....	23	16	84	17	33	11	64	14	153	15	357	15
Meningitis .....	41	28	209	42	126	42	202	44	769	77	1,347	56
Carditis .....	9	6	19	4	7	2	18	4	4	0	57	2
Respiratory .....	40	28	79	16	91	30	90	20	27	3	327	14
Rash .....	2	1	12	2	8	3	2	0	4	0	28	1
Nonspecific febrile illness .....	5	3	17	3	10	3	23	5	9	1	64	3
Sepsis .....	3	2	11	2	2	1	12	3	2	0	30	1
Other .....	21	14	53	11	23	8	47	10	24	2	168	7
Total .....	145	<sup>3</sup> 99	488	<sup>3</sup> 98	302	<sup>3</sup> 101	459	<sup>3</sup> 101	1,000	<sup>3</sup> 99	2,394	100
<i>NCMC</i>												
Encephalitis .....	1	3	1	1	2	2	2	1	5	4	11	2
Meningitis .....	4	11	18	13	14	12	18	11	19	17	73	13
Carditis .....	2	5	2	1	1	1	...	...	1	1	6	1
Respiratory .....	20	53	71	52	62	52	80	51	53	46	286	51
Rash .....	...	...	3	2	6	5	4	3	3	3	16	3
Nonspecific febrile illness .....	3	8	13	10	15	13	12	8	10	9	53	9
Gastrointestinal .....	2	5	6	4	2	2	14	9	11	10	35	6
Sepsis .....	...	...	8	6	5	4	13	8	5	4	28	5
Asymptomatic .....	1	3	2	1	2	2	2	1	1	1	8	1
Other .....	5	13	12	9	11	9	12	8	7	6	50	9
Total .....	38	<sup>3</sup> 101	136	<sup>3</sup> 99	120	<sup>3</sup> 102	157	100	115	<sup>3</sup> 101	566	100

<sup>1</sup> Includes only cases for which the clinical syndrome was reported.

<sup>3</sup> Does not add to 100 because of rounding.

<sup>2</sup> Percentages rounded to nearest whole percent.

Table 4. Clinical findings associated with Coxsackie B1–B5 infections

Sign or symptom	B1			B2		
	Number of cases reported	Number with Finding	Percent	Number of cases reported	Number with Finding	Percent
Fever .....	35	33	94	121	117	97
Biphasic .....	11	2	18	32	12	38
Pharyngitis .....	31	24	77	91	77	85
Vomiting .....	21	9	43	57	27	47
Headache .....	20	8	40	54	22	41
Respiratory .....	21	8	38	62	24	39
Diarrhea .....	16	4	25	55	17	31
Abdominal pain .....	15	0	0	53	15	28
Rash .....	15	1	7	54	15	28
Otitis .....	17	2	12	46	8	17
Abnormal mental status .....	39	10	26	140	17	12
Jaundice .....	15	0	0	48	3	6
Myositis .....	16	1	6	42	0	0

<sup>1</sup>  $P < .05$  by chi-square test, comparing rate for the individual B agent with the overall rate for the specific sign or symptom.

percent of B isolations were from patients 0–4 years old, and 25 percent were from those < 1 year. Laboratory personnel report that the predominance of young patients in this population could have been due at least in part to greater compliance by pediatricians than by internists in submitting specimens.

**Sex distribution.** In general, B agents were isolated more frequently from males than from females (table 2).

In the ESP population, of B isolations from patients whose age and sex were reported, 2,278 (59 percent) were from males and 1,574 (41 percent) from females. This male:female ratio of approximately 1.5:1 was seen for nearly all clinical syndromes and for most age groups. Several age groups had a male:female ratio significantly lower than expected: patients 20–29 years of age (0.9:1;  $P < .001$ ), those  $\geq 50$  years (0.8:1;  $P < .01$ ), and those < 1 year (1.3:1;  $P < .05$ ). The male:female ratio for the yearly age groups from 3 years to 8 years was higher than expected, ranging from 1.56:1 to 2.57:1; this greater male predominance was significant for the 4-, 6-, and 8-year groups ( $P < .05$  for each).

The sex distribution among NCMC patients (male:female ratio, 1.6:1) was similar to that found among ESP patients. The age-sex relationships were also similar.

## Clinical Results

**Associated clinical syndromes.** The most common B-associated syndrome reported through national surveillance (table 3) was meningitis (1,347 isolates; 56

percent of all isolates with known B-associated syndrome), followed by encephalitis (357; 15 percent), respiratory tract disease (327; 14 percent), nonspecific febrile illness (64; 3 percent), carditis (57; 2 percent), sepsis (30; 1 percent), rash (28; 1 percent), paralytic disease (16; 0.7 percent), and other known syndromes (168; 7 percent). The clinical syndrome was unknown for the remaining isolates. The syndrome distributions for most of the individual agents were similar. However, when the overall distribution of syndromes associated with Coxsackie B viruses was taken into account, B5-associated meningitis significantly exceeded expected values (77 percent versus 56 percent,  $P < .001$ ).

The distribution of clinical syndromes among the NCMC study population was different from that among the ESP-based population. With higher submission rates of specimens for viral isolation at NCMC, a much higher proportion of isolates was associated with respiratory tract disease (286 isolates; 51 percent). This was followed by meningitis (73; 13 percent), undifferentiated fever (53; 9 percent), gastrointestinal illness (35; 6 percent), sepsis (28; 5 percent), rash (16; 3 percent), encephalitis (11; 2 percent), asymptomatic cases (8; 1 percent), carditis (6; 1 percent), and other miscellaneous syndromes (50; 9 percent). The syndrome for the remaining isolates was unknown. The syndrome distribution was similar for each of the B agents.

**Clinical signs and symptoms.** The clinical signs and symptoms found among NCMC patients are shown in Table 4. Only those for whom the status of each sign or symptom was known are included in the denominator.

reported by the Nassau County Medical Center, 1970–79, by agent

B3			B4			B5			Total		
Number of cases reported	Number with Finding	Percent	Number of cases reported	Number with Finding	Percent	Number of cases reported	Number with Finding	Percent	Number of cases reported	Number with Finding	Percent
111	108	97	148	144	97	106	103	97	521	505	97
23	4	17	34	11	32	25	5	20	125	34	27
81	76	<sup>1</sup> 94	120	96	80	83	71	86	406	344	85
23	16	70	80	38	48	45	37	<sup>2</sup> 82	226	127	56
19	15	<sup>1</sup> 79	55	20	36	24	19	<sup>3</sup> 79	172	84	49
24	20	<sup>2</sup> 83	61	18	30	20	12	60	188	82	44
19	13	<sup>1</sup> 68	62	22	35	28	16	57	180	72	40
14	10	<sup>3</sup> 71	58	19	33	13	6	46	153	50	33
18	13	<sup>2</sup> 72	50	12	24	15	6	40	152	47	31
12	6	50	59	16	27	22	11	<sup>1</sup> 50	156	43	28
143	19	13	158	20	13	127	18	14	607	84	14
12	8	<sup>2</sup> 67	49	4	8	9	2	22	133	17	13
8	2	25	47	5	11	7	0	0	120	8	7

<sup>2</sup>  $P < .001$  by chi-square test.

<sup>3</sup>  $P < .01$  by chi-square test.

*'To our knowledge, this is the largest surveillance review of Coxsackie B viruses to date, with data from 10 years' surveillance in two different settings.'*

The most common finding was fever, reported in 97 percent of patients; it was described as biphasic in 27 percent of cases for which adequate information was available. Other frequently reported clinical findings included pharyngitis (85 percent), vomiting (56 percent), headache (49 percent), respiratory signs and symptoms (one or more of the following: cough, congestion, dyspnea, tachypnea, grunting respiration, retractions, inspiratory stridor, respiratory disease, or rhonchi; 44 percent), diarrhea (40 percent), abdominal pain (33 percent), rash (31 percent), and otitis (28 percent). B3 deviated most from the overall distribution for all agents combined, with significantly higher frequencies found for respiratory abnormalities, rash, and jaundice ( $P < .001$  for each); abdominal pain ( $P < .01$ ); and headache, pharyngitis, and diarrhea ( $P < .05$  for each). For B5, significantly higher rates of vomiting ( $P < .001$ ), headache ( $P < .01$ ), and otitis ( $P < .05$ ) were reported. For B1, a higher rate of mental status abnormality was reported ( $P < .05$ ).

Rash, reported in association with 31 percent of Coxsackie B1-B5 isolates, was seen significantly more frequently among younger patients (1-tailed Kolmogorov-Smirnov test,  $\chi^2 = 11.99$ ,  $df = 2$ ,  $P < .01$ ). No other sign or symptom was significantly associated with age.

Neither the maximum temperature (TMax) observed nor the total number of febrile days was statistically associated with age among this patient population. The proportion of those with TMax  $\geq 101^\circ\text{F}$  was similar for all reported syndromes except gastrointestinal disease: a significantly lower proportion of patients with this kind of disorder attained TMax  $\geq 101^\circ\text{F}$  (67 percent versus 88 percent;  $P < .05$ ).

The proportion of patients with TMax  $\geq 101^\circ\text{F}$  was similar for all the B agents except B1, for which there was a significantly lower proportion of such patients (81 percent versus 89 percent;  $P < .01$ ).

**Hospitalized patients.** Overall, 70 percent of the 624 NCMC isolates were from outpatients, and 30 percent were from inpatients (19 percent from those hospitalized 1 week or less and 11 percent from those hospitalized more than 1 week). Although the duration of hospitalization was not significantly associated with age, the proportion of those hospitalized was highly associated with

young age (by the Kolmogorov-Smirnov test,  $\chi^2 = 85.65$ ,  $df = 2$ ,  $P < .001$ ), and most of this was accounted for by the high rate of hospitalization among infants  $< 1$  year (64 percent among infants versus 30 percent among other age groups).

## Laboratory Results

**ESP isolations.** From 1970 through 1975, specimens submitted for virus isolation were coded as CSF (cerebrospinal fluid), non-CSF, or unknown. Of the agents isolated during this period, 588 (19 percent) were isolated from CSF and 2,350 (81 percent) from non-CSF specimens. In 1976, the range of specifically reported specimen sources was expanded. Of the agents isolated from 1976 through 1979, 152 (9 percent) were from CSF, 632 (39 percent) from throat swabs, 479 (30 percent) from stool specimens, 199 (12 percent) from rectal swabs, 40 (2 percent) from the nasopharynx, 28 (2 percent) from tissue specimens, 16 (1 percent) from urine, and 61 (4 percent) from other known sources. B5 was the agent most frequently isolated from CSF: there were 370 B5 isolations (23 percent of the total number of isolations from CSF) from 1970 through 1975 and 40 (16 percent of the total number of isolations from CSF) from 1976 through 1979. The actual success rate of CSF isolations of Coxsackie B agents is unknown because only successful enterovirus isolation attempts are reported through the ESP.

**NCMC isolations.** From 602 patients, a total of 624 B1-B5 agents were isolated (including mixed B infections). From these known infected patients, a total of 1,092 specimens were submitted, of which 767 (70 percent) were positive. The 1,092 specimens included 575 throat swabs, 269 rectal swabs, 163 nasopharyngeal swabs, and 85 CSF specimens. The overall rate of positivity, from all positive patients and from any day of illness, was 83 percent for throat swabs, 78 percent for rectal swabs, 39 percent for CSF, and 30 percent for nasopharyngeal swabs. These rates did not vary significantly among the different B agents.

The Virus Laboratory receives throat swabs from all ill pediatric inpatients and additional types of specimens as indicated—for example, CSF from patients with suspected meningitis or encephalitis. The laboratory does not define specific time periods beyond which certain specimens are discouraged. For example, throat and CSF specimens are not limited to the early phases of illness, when they are more likely to be positive.

Only for throat swabs was the positivity rate significantly correlated with the time after onset of illness at which the specimen was obtained. Peak positivity (91 percent) was on Day 3 of illness, regardless of clinical

diagnosis (by linear regression,  $z = -3.56$ ,  $P < .05$ , for throat positivity rates between Day 0 and Day 9). To correct for the possible bias that throat specimens were preferentially submitted early rather than late in clinical illness or that positive throat swabs were the most common mode of entry into the study, we examined the subset of patients with positive rectal swabs, that is, those who would have been entered into the study regardless of throat swab positivity. Again, throat swab positivity tended to be greatest during the early phases, peaking on Day 3 of illness. Among known positive patients from whom both specimens were submitted, the positivity rate for rectal swabs (182 of 237; 77 percent) was significantly higher than that for throat swabs (140 of 237; 59 percent;  $P < .001$ ).

On the average, the B agents grew most quickly from throat specimens. Of the 474 positive specimens, cytopathic effect (CPE) was noted within 5 days in 232 (49 percent). CPE within 5 days was especially common for B4 (82 of 133 specimens; 62 percent;  $P < .01$ ) and B1 (19 of 30 specimens; 63 percent; not statistically significant), but was significantly less common for B5 (27 of 84 specimens; 32 percent;  $P < .01$ ). CPE was not detected as quickly among positive specimens from other sites. Of 50 positive nasopharyngeal specimens, only 17 (34 percent) were positive within 5 days; 10 (30 percent) of 33 positive CSF specimens showed CPE within 5 days; and only 55 (26 percent) of rectal specimens were positive during this period. In comparison with positive specimens for all Coxsackie B viruses combined, B4 was detected significantly more quickly from a source other than the throat (within 5 days from rectal swabs; 46 percent for B4 versus 26 percent overall;  $P < .001$ ).

The positivity rate for a specific specimen source was occasionally, but not consistently, related to the clinical syndrome. For example, rectal swab positivity for reported gastrointestinal (GI) illness (17 of 24 specimens; 71 percent) did not differ from that for non-GI syndromes (196 of 248 specimens; 79 percent), reflecting the overall high rate of isolation from the lower alimentary tract, regardless of syndrome. On the other hand, isolation from the upper alimentary tract (throat or nasopharynx) was significantly more frequent for respiratory than for nonrespiratory tract disease (87 percent versus 60 percent;  $P < .001$ ).

## Discussion

To our knowledge, this is the largest surveillance review of Coxsackie B viruses to date, with data from 10 years' surveillance in two different settings. Although there were undoubtedly biases inherent in patient selection (especially in the ESP population), the predominance of young children among the two Coxsackie B-

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infected populations is consistent with previous reports (1-4). Young children are considered the largest reservoir and most active source of transmission of these agents, and —except for the youngest infants—they are most often asymptomatic or only mildly ill (13,35).

Older patients were relatively heavily represented among cases of more severe illness. This phenomenon has also been reported for poliovirus infections (1,36,37), in which the case:infection ratio and severity of clinical involvement increase with age. Although the precise reasons for this are not clear, clinical (38-40) and experimental animal (41) data for related enteroviruses suggest that heavy physical exertion may be a factor.

In general, one must be circumspect in interpreting clinical data from enterovirus-infected patients. Isolation of an enteroviral agent (especially from the alimentary tract) does not necessarily implicate that agent as the cause of disease, although if other possible diagnoses can be excluded, it is reasonable to assign it an etiological role.

The clinical syndromes described for the two populations differed. This fact reflected differences in selection of patients for viral culturing. Indeed, most infections are asymptomatic or produce only mild clinical illness (1, 2, 18), a picture seen more in the NCMC than in the ESP population. Results from the Virus Watch Studies conducted in the late 1960s (33, 34) suggest that severe clinical disease represents only "the tip of the iceberg" with respect to all enteroviral infections.

Laboratory data from NCMC suggest that both a throat and a rectal specimen are necessary to maximize the probability of isolating a B virus quickly and reliably from an infected patient. Throat swabs had the highest positivity rate, and B agents were most quickly grown from this source. However, rectal swabs were positive for a longer time after onset of clinical illness and were thus more reliable than throat swabs in ensuring isolation of a B agent.

On the basis of these data, it seems reasonable to recommend that both throat and rectal specimens be obtained from every patient for whom prompt yet reliable laboratory diagnosis of a B infection is sought. Throat specimens should be collected within the first

3–5 days of illness, if possible. Further data are required to determine whether these recommendations apply to the other enteroviral groups—Coxsackie A, echoviruses, polioviruses, and enteroviruses 68–72.

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